Proposed Decision Memo for Percutaneous Transluminal Angioplasty (PTA) and Stenting of the Renal Arteries (CAG-00085R4)

Decision Summary

The Centers for Medicare and Medicaid Services (CMS) proposes to make no change in the NCD addressing PTA of the renal arteries (Pub. 100-3, 20.7, B1).

We are requesting public comments on this proposed determination pursuant to Section 1862(l) of the Social Security Act. After considering the public comments, we will make a final determination and issue a final decision memorandum.

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Proposed Decision Memo

TO: Administrative File: CAG 00085R4

FROM:

Steve Phurrough, MD, MPA
Director, Coverage and Analysis Group

Marcel Salive, MD, MPH
Director, Division of Medical and Surgical Services

Sarah McClain, MHS
Lead Analyst

Lawrence Schott, MD, MS
Lead Medical Officer

SUBJECT: Proposed Coverage Decision Memorandum for Percutaneous Transluminal Angioplasty (PTA) and Stenting of the Renal Arteries

DATE: November 20, 2007

I. Proposed Decision

The Centers for Medicare and Medicaid Services (CMS) proposes to make no change in the NCD addressing PTA of the renal arteries (Pub. 100-3, 20.7, B1).

We are requesting public comments on this proposed determination pursuant to Section 1862(l) of the Social Security Act. After considering the public comments, we will make a final determination and issue a final decision memorandum.

II. Background

In approximately 90% of cases, renal artery stenosis (RAS) – unilateral or bilateral narrowing of the lumen of the renal arteries – is the result of generalized atherosclerosis, which progressively diminishes blood flow to the kidneys and may elevate blood pressure (BP) or impair functioning of the kidneys. Such atherosclerotic vascular narrowing, however, is a systemic disease that affects not only the kidneys but also the arteries supplying the heart, brain and other vital organs. Patients with RAS and generalized atherosclerosis more often die from cardiovascular causes such as a heart attack or stroke, rather than from kidney failure.

Overall, atherosclerotic RAS ranges in prevalence from about 30% in patients with coronary artery disease to about 50% in patients who are elderly or have diffuse atherosclerotic disease. The severity or percent RAS that is reported widely varies in clinical significance and is generally poorly correlated with a patient's kidney function. Measurement, for example, of the degree of narrowing and flow through the stenotic renal segment is imprecise and non-standardized, and there is no reliable diagnostic test or baseline characteristic that accurately predicts a patient's post-treatment kidney function outcome. Importantly, while RAS may occur in combination with hypertension and kidney disease, a stenotic renal vessel, in which plaque has partially blocked blood flow, may also be an incidental finding, may not be the cause of a patient's disease state, or may lie proximal to a chronically diseased kidney which is already beyond recovery. It is thus uncertain which patients will improve, remain unchanged, worsen or be harmed following treatment.

Based upon each patient's presenting history, the treatment options for atherosclerotic RAS presently include aggressive medical therapy administered alone or in combination with endovascular therapy and/or open surgical reconstruction of one or both renal arteries. Triple medical therapy with antihypertensive, antihyperlipidemic and antiplatelet drugs consists of multiple antihypertensive agents prescribed to lower blood pressure, statins to lower low density lipoprotein (LDL) cholesterol and stabilize plaques, and antiplatelet agents to reduce thrombosis (clotting of the arteries). While the current NCD addresses angioplasty, at present, nearly all endovascular renal artery procedures utilize angioplasty with stent placement across the narrowed vessel. Surgical renal artery reconstruction is typically reserved for concomitant pararenal abdominal aortic reconstructions for aortic aneurysms or severe aortoiliac occlusive disease, complicated renal artery anatomy or aneurysms, and/or repair of endovascular interventions that have resulted in chronic restenosis or are acutely complicated by dissection, thrombosis, perforation or bleeding. Angioplasty with and without stenting and surgical reconstruction all fall within the term "renal artery revascularization (RAR)."

Endovascular and surgical interventions incur procedural risks with potential for morbidity and mortality. The most common major complication of percutaneous procedures is acute renal failure. Other complications include contrast-induced nephropathy, dissection, thrombosis, segmental infarction, perforation, bleeding, and renal and systemic atheroembolization, especially in patients with concomitant advanced aortoiliac disease. Surgery additionally incurs all the risks of a major abdominal procedure.

Considering the general uncertainty regarding evaluation and management of patients with atherosclerotic RAS, as well as controversy about the balance of risks and benefits for alternative medical, surgical and endovascular treatments, CMS opened this national coverage analysis to evaluate Medicare coverage policy for renal artery revascularization procedures.

III. History of Medicare Coverage

History of Medicare Coverage for Percutaneous Transluminal Angioplasty

As described in paragraph 3 of section B1 of the Medicare National Coverage Determination (NCD) Manual for PTA (20.7), since at least 1994 percutaneous transluminal renal angioplasty (PTRA) has been nationally covered to treat atherosclerotic obstructive lesions:

“Of the renal arteries for patients in whom there is an inadequate response to a thorough medical management of symptoms and for whom surgery is the likely alternative. The PTA for this group of patients is an alternative to surgery, not simply an addition to medical management.”[1]

Benefit Category Determination

For an item or service to be covered by the Medicare program, it must meet one of the statutorily defined benefit categories outlined in the Social Security Act.

Surgical renal artery reconstruction and percutaneous transluminal renal angioplasty with or without stenting fall under the benefit categories set forth in section §1861(b)(3) (inpatient hospital services), a part A benefit under §1812(a)(1), and §1861(s)(1) (physician services), a part B benefit. This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

February 26, 2007	CMS internally generated national coverage analysis (NCA) and initiated reconsideration of current coverage policy for PTA of the renal arteries.
July 18, 2007	MedCAC considered PTA and stenting of the renal arteries.

November 20, 2007	Proposed decision memorandum posted; 30-day comment period begins.

V. FDA Status

Renal stents are class III devices[2,3] which require premarket approval (PMA) and for which documentation, including engineering and clinical data, must be submitted demonstrating that the data and information in the application constitute valid scientific evidence and provide reasonable assurance that the device is safe and effective for its intended use.[4,5]

The FDA (2002) issued two PMA marketing clearances for renal stents (P890017/S010 and P020007), each subject to conditions of approval and indicated for use only in patents with atherosclerotic disease of the renal arteries following suboptimal or failed PTRA of de novo or restenotic lesions.[6,7] Neither of these PMAs for stenting following suboptimal or failed PTRA was reviewed by the FDA’s Circulatory System Devices Panel. These stenting devices are no longer being marketed, and there are presently no FDA approved devices for primary stenting or distal embolic protection in the renal arteries.

The FDA’s Manufacturer and User Facility Device Experience (MAUDE) database for medical device adverse event reporting suggested (2006) that “virtually all of the renal stenting procedures currently conducted in the U.S. are performed using stents not indicated for use in the renal vasculature, most commonly including biliary stents. Biliary stents are Class II devices under the FDA's risk-based classification system and are marketed under the premarket notification (510[k]) pathway. Biliary stents are not indicated for use in any part of the vasculature (unless a separate PMA has been approved for such use) and are typically indicated only for palliative treatment of malignant neoplasms in the biliary trees of patients with terminal cancer. As a result of the risk/benefit profile for these patients, marketing clearance under 510(k) requires minimal evaluation of long-term performance characteristics such as stent durability. Clinical data are only provided in unusual cases and, for a biliary stent, would be unrelated to renal artery stenosis.”[8]

In 2003 the FDA issued a 510(k) approval letter (K033394) for the PALMAZ GENESIS transhepatic biliary stent (Cordis), indicated for use only in palliation of malignant neoplasms in the biliary tree, with the following limitation:

“The Office of Device Evaluation has determined that there is a reasonable likelihood that this device will be used for an intended use not identified in the proposed labeling and that such use could cause harm. Therefore, in accordance with Section 513(i)(1)(E) of the Act [Federal Food, Drug and Cosmetic Act], the following limitation must appear in the Warnings section of the device’s labeling:

The safety and effectiveness of this device for use in the vascular system have not been established.”

[According to the published study design, all patients in the stent therapy arm of the ongoing “Cardiovascular Outcomes in Renal Atherosclerotic Lesions” (CORAL) trial will undergo implantation of a Cordis Genesis stent.[9]]

On May 4, 2004, a Class I recall was initiated for the PRECISE RX Nitinol Stent transhepatic biliary stenting system (Cordis) with the following “Reason for Recall” on the FDA’s website:

“Some physicians use this device for vascular use. This use has not been cleared by the FDA. When used this way, air may be introduced into the patient via the stent system causing serious problems including coma, seizure and stroke. There have been nine patient injuries due to air embolism and seven incidents of malfunction in connection with the use of this system outside of its approved indications. Cordis is recalling its revised instructions for use and strongly recommends that physicians limit the use of the PRECISE RX Stent to FDA-approved uses only.”[10]

VI. General Methodological Principles

When making national coverage decisions, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

A detailed account of the methodological principles of study design that the agency utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix A. In general, features or clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

Public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum.

VII. Evidence

A. Introduction

This summary represents the body of evidence evaluating renal artery revascularization for the treatment of patients with atherosclerotic RAS. The discussion of evidence reviewed focuses upon whether the body of evidence is adequate to draw conclusions about the health benefits of these interventions compared to aggressive medical therapy alone, as well as whether the body of evidence is generalizable to and demonstrates improved health outcomes for Medicare patients.

In this proposed decision memorandum, the key health outcomes of most interest to CMS are kidney function, cardiovascular event rates, mortality and quality of life.

Of lesser weight and value to CMS are post-procedural patency rates reflecting frequency of restenosis (recurrent narrowing greater than an arbitrary 50% threshold of a treated vessel after intervention), as well as surrogate endpoints such as patients' blood pressure (BP).

"Control of BP is actually a very soft endpoint most often measured by a combination of the decrease in BP and an alteration in the number of drugs used to control the high BP. This means of evaluation is insufficient because physicians will often exchange three or four less-effective drugs for one or two more powerful or appropriate drugs, and suddenly the BP will be more effectively controlled, but simultaneously a renal artery stent had been used, or the change in drugs might occur after the stent had been placed. The result is that it would appear as if the stent were responsible for the improved BP control, when in fact the change might be due in part or in toto to the altered drug regimen."[11]

B. Discussion of evidence reviewed

1. Literature Search

In addition to AHRQ's extensive search for relevant research designs (excluding abstracts) in the MEDLINE database from inception to April 23, 2007, CMS searched PubMed (1990 to present) for all RCTs evaluating medical, endovascular or surgical treatments with RAS. Studies must have presented original data for adult humans and been published in peer-reviewed English language journals.

Six randomized controlled trials were identified. Three[12,13,14] of those RCTs were evaluated in the 2003 Cochrane review, and two[15,16] of those three were evaluated in AHRQ's 2006 and updated 2007 comparative effectiveness reviews.

2. External technology assessments and clinical reviews

Cochrane (2003)

Selection criteria for the 2003 Cochrane Collaboration systematic review included randomized and quasi-randomized controlled trials that compared angioplasty with medical therapy in hypertensive patients with renal artery stenosis of > 50% reduction in luminal diameter and at least six months follow-up. Three trials involving a total of 210 patients met the review's inclusion criteria but only 4 patients in those trials were stented - none in Webster (1998), 2 patients in Plouin (1998), and 2 patients in van Jaarsveld (2000).

The Cochrane review found available data insufficient to conclude that balloon angioplasty without stenting was superior to medical therapy in lowering BP of atherosclerotic RAS patients in whom BP could be pharmacologically controlled. In patients with hypertension refractory to medical therapy, there was weak evidence that angioplasty lowered BP more effectively than medical therapy. There were no differences between treatments in renal function.[17]

AHRQ (2006 and 2007)

AHRQ's original 2006 Comparative Effectiveness Review (CER) noted there was no published evidence directly comparing angioplasty with stenting versus aggressive medical treatment with currently available drugs for atherosclerotic RAS.[18]

AHRQ's search strategy was extensive and comprehensive. In its 2006 search, AHRQ identified 2163 citations in the scientific literature. Members of its Technical Expert Panel and other domain experts contributed 28 additional articles for consideration. An updated 2007 search yielded 185 new citations, nine of which met AHRQ's eligibility criteria for inclusion.[19]

As in the original CER, none of the additional nine publications evaluated relative effects of intensive medical therapy and angioplasty with stent for atherosclerotic RAS. AHRQ reiterated in 2007 that overall study quality remained limited by inadequate reporting and/or data collection, incomplete analyses and inconsistent use of interventions such as combining angioplasty with and without stent, limited or difficult assessment of applicability due to restrictive patient eligibility or inadequate reporting, inconsistent outcome metrics, and limited statistical power due to small sample size.

AHRQ's 2007 update described the following findings:

- Almost two-thirds of studies were of poor methodological quality and more than half were of limited applicability to the population of interest.
- No RCTs compared angioplasty with stent and aggressive medical treatment with ACE inhibitors, statins, and anti-platelet drugs (Tier I studies[20]).
- The two most relevant RCTs (Tier II studies: Webster 1998 and Plouin 1998) did not compare interventions that are currently used for patients with RAS. Only 2 patients in Plouin's (1998) RCT received stents and ACE inhibitors were rarely employed.
- Other comparative studies (Tier III) were methodologically flawed or did not compare angioplasty and medical treatment.
- There were a substantial number of cohort studies (Tier IV) that prospectively evaluated angioplasty with stent, but very few cohort studies of medications - none of which explicitly evaluated aggressive medical treatment with ACE inhibitors, statins, and anti-platelet drugs. Thus, indirect comparisons across the cohort studies were limited.
- Among the comparative studies there was some evidence of a relative benefit in BP after angioplasty, particularly in patients with bilateral disease; however, this conclusion was based largely on the end-of-study (not primary endpoint after which some treatment cross-over occurred) of one RCT (Webster 1998) and either clinically though not statistically significant differences, partially statistically significant differences, or nonrandomized trial data.
- Among the comparative studies there was no difference in kidney function outcomes. Studies generally included too few patients and were of too short a duration to make definitive assessments regarding differences in clinical event outcomes of interest: mortality, cardiovascular event rates, and quality of life.

- Although studies were generally too small to detect any but large differences in mortality rates, no differences in mortality were found between interventions, up to about 5 years. Very high mortality rates, over 40 percent within 6 years, occurred mostly in studies of patients with either high-grade stenosis (> 75%) or bilateral disease.

- Direct and indirect comparisons of interventions generally found no clinical or statistically significant differences in kidney outcomes. However, only in some of the angioplasty with stent placement studies did patients have improved kidney function. That implied that, at least in a (poorly described) subset of patients with atherosclerotic RAS, kidney function was more likely to improve after angioplasty with stent placement than with continued medical treatment.

- Both trials and most of the other comparative studies found some evidence of greater BP improvement after angioplasty than with medical treatment; although the benefit of angioplasty may be limited to patients with bilateral disease. In contrast, cohort studies of angioplasty generally found somewhat lower reductions in BP (6-32/0-17 mm Hg) than cohorts of medical interventions (20-50/8-42 mm Hg), though it was not possible to draw conclusions about the relative effect on BP measurements of different interventions.

- Comparative studies found similar rates of cardiovascular disease regardless of intervention, though these studies were not designed to find significant differences in cardiovascular events. The data from cohort studies on cardiovascular events were too sparse to draw conclusions.

- A single trial (Krijnen 2005) found no consistent difference in quality of life between angioplasty and medical therapy.

- Adverse events, variably defined, occurred in up to 13% of patients receiving angioplasty, though serious long-term adverse events were rare. Reported adverse events from antihypertensives were relatively minor and transient.

- A variety of indicators of the severity of atherosclerotic RAS and of health problems, such as poorer kidney function, severity of stenosis, and coexisting cardiovascular disease predicted poorer outcomes in patients with atherosclerotic RAS. The reviewed studies did not report any indicators that may predict improved outcomes. Two trials found that patients with bilateral RAS had better outcomes after angioplasty than medical therapy, compared to patients with unilateral disease.

- In comparative studies, captopril test, renogram, recent hypertension, and stenosis greater than 80% were not predictors of either worse outcome overall or of which intervention would result in better outcomes. Among patients receiving angioplasty, there was little consistent evidence about which diagnostic tests would predict more favorable outcomes. Two studies found that Doppler ultrasonography findings were predictive of outcomes after angioplasty, but they disagreed as to whether resistive index predicted worse or better outcomes.

- No study that met eligibility criteria reported analyses of whether periprocedural interventions, such as different drugs or different approaches, affected either complications or long-term outcomes.

AHRQ (2007) also made these conclusions about the evidence:

“The evidence does not support one treatment approach over the other for the general population of people with ARAS.

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- Weak evidence suggests no difference in mortality rates.

- There is acceptable evidence that, overall, there is no difference in kidney outcomes between patients treated medically only and those receiving angioplasty without stent, although the relevance of this finding to current practice is questionable due to changes in treatment options. However, improvements in kidney function were reported only among patients receiving angioplasty.

- There is acceptable evidence that combination antihypertensive treatment results in large decreases in blood pressure, but there is inconsistent evidence regarding the relative effect of angioplasty and medication on blood pressure control.

- There is weak evidence suggesting similar rates of cardiovascular events between interventions; however, it is likely that the studies were too small to detect different rates of cardiovascular events.

- Weak evidence suggests no difference in QoL with medical treatment alone or with angioplasty.

- The evidence does not adequately assess comparisons of adverse events between medical treatment alone and angioplasty.
- There is weak evidence that patients with bilateral RAS may have more favorable outcomes with angioplasty than medical therapy.
- Weak or inconsistent evidence does not support statements on whether other clinical features (such as demographics or indicators of RAS severity) or diagnostic tests predict whether patients would have better clinical outcomes with angioplasty or with medical therapy alone.
- There is no evidence regarding the value of periprocedural interventions with angioplasty."

3. Internal technology assessment

Cochrane and AHRQ have reviewed the breadth of evidence for treatment of atherosclerotic RAS. We will not repeat that review here. However, CMS identified a total of 6 RCTs that evaluated surgical, medical and/or endovascular treatments for atherosclerotic RAS. The results are tabulated below and subsequently described.

Table 1. Published Randomized Controlled Trials (RCTs)

RCT	Patient Demographics	Pts Stented	Endpoints	Comments
Weibull (1993)	N = 58 (all unilateral RAS)	0	Surgical group better primary patency rate, not secondary patency rate	Relatively young, nondiabetic pts randomized betw April1984 and February 1990

RCT	Patient Demographics	Pts Stented	Endpoints	Comments
	N = 29 PTRA N = 29 Surg.RAR		NS in primary or secondary results for BP response or renal function following all additional therapy after restenoses	5/29 pts (17%) in PTRA group, and 9/29 pts (31%) in surgical group had major complication but the frequency of major and minor complications did not significantly differ betw groups in this small trial
Webster (1998) “SNRASCG”	N = 135 total pts (multicenter) 80 pts nonrand 55 pts rand N = 25 PTRA N = 30 med. tx (28 bilateral and 27 unilateral RAS)	0	NS in unspecified office BP (at 6 month 1º endpoint)	No pts stented Did not allow ACE inhibitors Dates of trial recruitment and randomization were unstated
Plouin (1998) “EMMA”	N = 59 (all unilateral RAS) N = 23 PTRA(S)	2	NS in mean ambulatory BP (at 6 month 1º endpoint)	Only 2 pts stented Used enalapril in only some pts

RCT	Patient Demographics	Pts Stented	Endpoints	Comments
	N = 29 medical tx			Trial recruitment between Jan 1992 and June 1995
van de Ven (1999)	N = 84 N = 42 PTRA(S) N = 42 PTRAS	(12) 42	PTRAS had better vascular patency than PTRA NS clinically	Intention to treat showed no change in clinical results at 6 months for PTRA or PTRAS Trial recruitment between Dec 1993 and March 1997
van Jaarsveld (2000) "DRASTIC"	N = 106 total pts (77-78% unilat RAS) N = 56 PTRA(S) N = 50 medical tx	2	NS at 12 month mean office SBP or DBP, daily drug doses or renal function	54 pts angioplasty alone; 2 pts stented 22 patients crossed over after 3 months and had received angioplasty Studied betw Jan 1993 and Nov 1998
Uzzo (2002)	N = 52 N = 25 Surg.RAR N = 27 medical tx	0		

RCT	Patient Demographics	Pts Stented	Endpoints	Comments
			NS identified between surg. and medical outcomes	Pts randomized to surgical RAR and medical mgmt over unspecified 8 year period

(NS = No statistically significant difference)

Weibull, et al. (1993)

Weibull and colleagues' trial (Sweden) compared renal angioplasty without stenting (PTRA) versus surgical reconstruction as initial therapy for unilateral RAS and measured technical results (primary and secondary patency) as well as effects on BP and renal function. Patency was defined as < 50% RAS not requiring reintervention. Patients with $\geq$ 50% restenosis underwent repeated interventions with PTRA or surgery. Primary results were for therapeutic effect achieved after the first performed intervention, and secondary results were for effect achieved following addition of all therapeutic efforts after restenoses, including 4 PTRA patients who required surgery and 1 surgical patient who underwent PTRA. All patients' cases were discussed by a surgeon, interventional radiologist and endocrinologist; and following consensus that both PTRA and surgery were possible on the basis of morphologic appearance, a patient was randomly assigned to a treatment group. Fifty-eight non-diabetic patients $\leq$ 70 years of age with severe hypertension (untreated BP $\geq$ 160 mm Hg), serum creatinine < 300 mmol/L and significant unilateral atherosclerotic RAS (main RAS diameter $\leq$ 2 mm and renal vein renin ratio of stenotic to nonstenotic side $\geq$ 1.5) within 1 cm from the aorta were randomized to PTRA (N = 29, median age 60, range 41–69 years) or to surgery (N = 29, median age 54, range 38-70 years). BP, renal function and angiography (to document renal artery patency) were obtained at 10 days, 1 year and 2 years after PTRA or surgery. Treatment was "technically successful" (defined as total elimination of the stenosis) in 24 of 29 (83%) of PTRA patients and in 97% of surgical patients (28 reconstructions were patent and 1 occluded), which did not represent a significant difference between groups. In technically successful cases, the primary patency rate after 2 years was 75% (18 of 24 patients) for de facto treated arteries in the PTRA group (62% for "intention to treat") and 96% in the surgical group (27 of the 28 successful revascularizations were patent), which represented a statistically significant difference (p = .05).

At the end of follow-up after all redo procedures, the secondary renal artery patency rate was 90% in the PTRA group and 97% in the surgical group, which was not a statistically significant difference. Primary and secondary results for both BP and renal function showed no significant differences between the PTRA and surgical groups. Acknowledging that the series consisted of highly selected, relatively young non-diabetics with renovascular hypertension and unilateral RAS admitted to the referral center, Weibull, *et al.* (1993) thought "from a technical point of view, the results should be the same with unilateral or bilateral lesions" and concluded that PTRA should be the first choice of therapy for atherosclerotic RAS causing renovascular hypertension "if combined with intensive follow-up and aggressive reintervention" with PTRA or surgical reconstruction.[21]

Webster, et al. (1998)

Webster and colleagues' Scottish and Newcastle Renal Artery Stenosis Collaborative Group (SNRASCG) multicenter trial compared the effects on BP and renal function after renal angioplasty without stenting (PTRA) versus medical therapy in hypertensive patients with both unilateral (N = 27) and bilateral (N = 28) stenoses in the randomized groups. A total of 135 eligible patients were identified, and the majority were not randomized. Only 55 of SNRASCG patients (mean age 61, range 40-75 years) with resistant hypertension (sustained hypertension diastolic BP $\geq$ 95 mm Hg on at least two anti-hypertensive drugs) and $\geq$ 50% RAS defined by angiography were randomized to either PTRA (N = 25, including 12 bilateral and 13 unilateral stenoses) or medical therapy (N = 30, including 16 bilateral and 14 unilateral stenoses). All patients were observed during an initial 4-week run-in period on a fixed drug regimen and subsequent changes were measured from the 4-week baseline. Results showed a "consistent, clinically important fall in BP in all groups between referral and end of the run-in phase." In 12 patients with bilateral RAS randomized to angioplasty, no significant change in systolic or diastolic BP was noted at the study's 6 month primary endpoint compared to 16 patients treated medically. A statistically significant ($P < 0.05$) decrease in office systolic BP was reported at the "latest follow-up" that widely ranged from 3-54 months. In unilateral RAS patients, no statistically significant or clinically important differences in outcome were observed between groups; and "if anything, the systolic BP fell more in the medical than in the intervention group." In the study's 80 nonrandomized patients, "no important differences were observed between the intervention patients and the medical patients, either at 6 months or most recent follow-up." There were also no significant differences or trends in serum creatinine observed between or within the angioplasty and medical groups during follow-up.

The SNRASCG study found no statistically significant difference in BP change between the angioplasty and medical groups at the study's 6 month primary endpoint for either bilateral RAS or unilateral RAS randomized patients. Following PTRA, no patient's hypertension was cured (defined as achieving normal BP off all drug therapy); there was no demonstrable benefit in terms of renal function or event-free survival; and "complications of the procedure were an important source of morbidity, even in the hands of experienced radiologists in specialist centers." The SNRASCG (1998) investigators additionally discussed that:

"Unfortunately there has been a lack of standardization of the methods of BP measurement, and critically, a failure to take into account regression to the mean from the time of referral. Our data demonstrate very clearly the substantial fall in BP that can be observed simply by a short period of structured follow-up with no intervention or change of therapy, even in patients who may have been in regular attendance at hypertension clinics. This run-in period to establish a baseline is an essential part of any study to evaluate changes in BP and is just as important in a trial of intervention as it would be in a trial of a new anti-hypertensive drug."[22]

Plouin, et al. (1998)

Plouin and colleagues' EMMA (French) multicenter trial was designed to evaluate the efficacy and safety of angioplasty for lowering BP in patients less than 75 years old (N = 49, mean age 59) with unilateral atherosclerotic RAS. After a 2-6 week run-in period on a standardized stepwise antihypertensive regimen, patients were hospitalized and randomized during qualifying angiography (all patients were angiogrammed and had their renal arteries classified into five grades: no stenosis, < 60%, 60-75%, > 75%, thrombosis) to continued antihypertensive drug therapy (N = 26) or to angioplasty (N = 23, including 2 with stenting). In the medical treatment group, 13 patients had a grade 60-74% RAS and 13 patients had "high-grade" ≥ 75% RAS. In the angioplasty group, 15 patients had a grade 60-74% RAS and 8 patients had "high-grade" ≥ 75% RAS. In patients randomized to angioplasty, antihypertensive drug therapy was stopped post-procedure but was resumed if hypertension persisted. The study's primary endpoint was 24 hour ambulatory blood pressure (ABP) determined at termination. Termination took place 6 months following randomization or earlier in patients who developed refractory hypertension defined as diastolic BP > 104 mm Hg. The study's secondary endpoints were treatment score (defined as number of antihypertensive agents administered) and incidence of complications. Two medical patients and 6 of 23 (26%) angioplasty patients suffered angiographic or procedural complications including 1 dissection with segmental renal infarction and 3 restenoses in the angioplasty group, which the authors found to be "substantial and higher than in many retrospective series." Early termination was required for refractory hypertension in 7 patients in the medical group, and the antihypertensive treatment was resumed in 17 patients in the angioplasty group.

Mean ABP at study termination, the study's primary outcome measure, did not significantly differ between the medical therapy and angioplasty groups. The EMMA (1998) investigators concluded that angioplasty is a drug-sparing procedure that involves some morbidity in patients with unilateral atherosclerotic RAS, but that "previous uncontrolled and unblinded assessments of angioplasty overestimated its potential for lowering BP." The authors also concluded that "most patients undergoing angioplasty still needed antihypertensive agents 6 or 12 months after the procedure" and that "reduction in treatment required by patients undergoing angioplasty should therefore be weighed against the risks of complications and restenosis."[23]

van de Ven, et al. (1999)

van de Ven and colleagues' single center trial (Netherlands) compared PTRA (N = 42, mean age 64.8 years) with PTRAS (N = 42, mean age 65.6) in hypertensive patients (BP > 160/95 with or without medication) who had ostial atherosclerotic RAS within 1 cm of the aortic lumen. Block randomization was utilized to balance intake in each treatment arm. About 20% of patients had prior PTRA and both treatment groups had a similar distribution of unilateral and bilateral RAS. Secondary PTRAS was allowed if PTRA failed either immediately (≥ 50% restenosis by elastic recoil) or during 6 month follow-up. Primary success rate (< 50% restenosis) following PTRA was 57% (24 of 42 patients) compared to 88% (37 of 42 patients) after PTRAS. At 6 months renal angiography was repeated, and the primary patency rate was 29% for PTRA and 75% for PTRAS. Restenosis after a successful primary procedure occurred in 48% of PTRA patients and 14% of PTRAS patients. Twelve PTRA patients underwent secondary stenting for primary or late failure of PTRA within the 6 month follow-up period, and primary PTRAS versus primary PTRA plus PTRAS as rescue therapy had similar outcomes. Evaluation based on intention-to-treat analysis showed no statistically significant difference in clinical results at 6 months for PTRA or PTRAS. Procedural complications (nearly identical for both groups) included bleeding (19%), femoral artery aneurysm (5%) and renal artery dissection/occlusion/thrombosis (5%), as well as cholesterol embolism in 4 of 42 patients (10%) in each treatment group. Renal failure induced by cholesterol embolism, defined as at least 20% increase in plasma creatinine concentration maintained for 1 month or longer, occurred in 3 of the 4 patients with embolism in the PTRAS group and in 2 of the 4 patients with embolism in the PTRA group.

van de Ven, *et al.* (1999) thought that PTRAS was a better technique than PTRA to achieve vascular patency in ostial atherosclerotic RAS and, considering the burden of reintervention after PTRA, that "primary PTRAS is a better approach to use." However, the authors discussed that while PTRAS may give patients a better start, long term follow-up would be needed to assess whether renal stenting is beneficial in terms of renoprotection; and the investigators concluded:

“Whether patients with ostial atherosclerosis renal artery stenosis should be treated at all is unclear. Ischemic nephropathy is a multifactorial disease, involving stenosis related ischemia and factors such as dyslipidemia, nephrosclerosis, cholesterol embolism, and in areas of advanced renal perfusion, the effect of hypertension. In cases of advanced renal dysfunction, whether restoration of renal perfusion is sufficient to avert deterioration in the long term is also unclear. Complications of PTRAS in these patients, many of whom have widespread atherosclerosis disease, are severe and include a substantial incidence of procedure-related dialysis dependency and death... We believe that a prospective comparative study of PTRAS and medical treatment will show which groups of patients should receive PTRAS.”[24]

van Jaarsveld, et al. (2000)

van Jaarsveld and colleagues’ large Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) trial screened 1205 patients at 26 centers and randomly assigned 106 hypertensive patients (mean age 60, range 18-75 years) with normal or mildly impaired renal function (serum creatinine $\leq$ 2.3 mg per dl) and unilateral or bilateral atherosclerotic RAS ($\geq$ 50%) to PTRA (N = 56) or medical therapy (N = 50). The trial evaluated particularly unilateral stenosis, including 43 of 56 patients (77%) in the angioplasty group and 39 of 50 patients (78%) in the medical therapy group with unilateral RAS. Patients were included who had diastolic BP $\geq$ 95 mm Hg despite treatment with 2 antihypertensive drugs or an increase of $\geq$ 0.2 mg per dl in serum creatinine during therapy with an ACE inhibitor. There was no run-in period. Mean office systolic and diastolic BP (primary outcome measures), doses of antihypertensive drugs and renal function were assessed at 3 and 12 months. Renal artery patency was assessed at 12 months.

At the end of the randomized portion of the DRASTIC trial at 3 months, results showed no significant change between groups in mean systolic or diastolic BP. Due to persistent hypertension despite treatment with $\geq$ 3 drugs or because of deterioration in renal function, 22 patients in the medical group underwent angioplasty (44% crossover) after 3 months; but according to intention-to-treat analysis, there were no significant differences between groups at 12 months for either systolic or diastolic BP, daily drug doses or renal function. While the study’s crossover limitations were discussed, the DRASTIC (2000) investigators nonetheless concluded that angioplasty had “little advantage over antihypertensive-drug therapy” for the treatment of hypertensive patients with RAS. Discussing the concept of hemodynamically significant stenosis, the authors also noted no correlation between BP response and baseline severity of RAS.[25]

Uzzo, et al. (2002)

Uzzo and colleagues' trial (USA) compared differences in event-free survival between RAS patients managed medically (N = 27) and surgically (N = 25) over 8 years at the Cleveland Clinic (median follow -up was 74 months overall and 85 months for survivors). Surgical management consisted of revascularization by a single surgeon and included aortorenal bypass (6), splenorenal bypass (3), hepatorenal bypass (8), ileorenal bypass (6), endarterectomy (1) plus aortic replacement with renal artery reimplantation (1). Prior to randomization, patients required angiographic confirmation of bilateral RAS involving > 75% of the luminal diameter, high-grade (> 75%) disease involving a solitary kidney, or unilateral high grade (> 75%) stenosis with azotemia defined as serum creatinine > 1.5 mg/dL and glomerular filtration rate (GFR) < 70 mL per minute. Exclusion criteria were baseline serum creatinine > 4.0 mg/dL, BP poorly controlled (DBP > 100 mm Hg) despite adequate medical management or comorbid conditions that prohibited ability to tolerate surgical revascularization. Follow-up was quarterly for the first 2 years, then every 6 to 12 months thereafter. Once a patient reached a stop point event, follow-up was yearly until the time of death. Repeat angiography was performed for 20% increase in serum creatinine over baseline, 20% decrease in GFR from baseline, > 1 cm decrease in kidney size, or evidence of functional deterioration on renal nuclear scan. The trial's primary endpoint was a comparison of stop point events between medical and surgical groups, defined as: (1) the development of poorly controlled hypertension (DBP > 100 mm Hg) despite adequate medical management, (2) "creatinine failure" as defined by reduction in GFR ≥ 50% from baseline, rise in serum creatinine > 4 mg/dL (5 mg/dL if baseline serum creatinine was between 2 and 4 mg/dL), doubling of serum creatinine from baseline, or development of end-stage renal disease requiring dialysis, (3) the development of an intercurrent "atherosclerotic" event such as a myocardial infarction or cerebrovascular accident, or (4) death. A total of 67% of patients (35/52) reached an endpoint, including 67% (18/27) in the medical group and 68% (17/25) in the surgical group.

There were no statistically significant differences in baseline demographics between the two groups, and results showed no statistically significant differences in the endpoints reached between groups. There were no statistically significant differences in death-free survival, dialysis-free survival or BP control. Cox proportional hazard survival analyses of interacting baseline demographic factors with likelihood of reaching an endpoint failed to identify statistically significant differences between groups at the 95% confidence interval, and analysis of variance comparing changes in GFR over time between groups likewise yielded no statistically significant differences. Uzzo, *et al.* (2002) acknowledged that the power of their study was limited by its small sample size (N = 52), that the power to detect even a large group difference such as a twofold change in median survival was only 53%, and that this "underscores the importance of large-scale prospective cooperative studies on the subject."[26]

4. MedCAC

On July 18, 2007, the Medicare Evidence Development & Coverage Advisory Committee (MedCAC) met to discuss the body of evidence, hear presentations and public comment, and make recommendations to CMS regarding currently available endovascular and surgical co-interventions for the treatment of patients with atherosclerotic RAS. The results of a technology assessment performed by the Tufts New England Medical Center Evidence-Based Practice Center were presented by Dr. Balk, and the panel heard presentations from Dr. Cooper, Dr. Dworkin, Dr. Sos and Dr. Linas.

Ten speakers, including professional society representatives and a manufacturers' representative, addressed the MedCAC panel. At the request of the committee chair following the public comment portion of the meeting, Dr. Cavanaugh of the FDA addressed the current status of FDA approval for devices used to stent renal arteries.

The panel conducted subsequent extensive discussion, as well as a question and answer period with the presenters and speakers; and the panel formally voted on following questions.

MedCAC Voting Questions

On a scale from 1 to 5, where **1 = not confident, 3 = uncertain** and **5 = highly confident**, the MedCAC panel voted upon three multiple part questions. The overall average score is tabulated below following each subpart of the questions.

For the treatment of patients with atherosclerotic RAS, how confident are you that the evidence is adequate to draw conclusions about safety and clinical effectiveness of the following renal artery interventions:

a) Surgical renal artery reconstruction (RAR)?	**2.92**
b) PTRA without stent placement?	**2.92**
c) PTRAS with bare metal stents?	**2.85**
d) PTRAS with drug-eluting stents?	**1.00**

Based on the evidence presented, how confident are you that the published results apply to:

a) Medicare patients with typical comorbidities?	**3.69**

b) Providers (facilities/physicians) in community practice?	**2.15**
c) Patient subgroups not represented in the study populations?	**1.69**

Based on the evidence presented for patients with atherosclerotic RAS, how confident are you that compared to aggressive medical treatment alone there are improved key health outcomes attributable to the following co-interventions:

a) Surgical renal artery reconstruction (RAR)?	**2.31**
b) PTRA without stent placement?	**2.08**
c) PTRAS with bare metal stents?	**3.15**
d) PTRAS with drug-eluting stents?	**NA** (evidence not adequate)

Where **1 = strongly agree, 2 = agree, 3 = uncertain, 4 = disagree** and **5 = highly disagree**, the MedCAC panel voted upon and a mean score recorded for the following final question.

Based on the evidence presented, should Medicare national coverage of any non-medical treatments for atherosclerotic RAS be limited only to patients enrolled in qualified clinical research studies? **2.23**

After the voting, additional discussion focused upon discussion questions about the strengths, weaknesses and practical issues regarding randomized trials. A scoresheet containing votes of all panelists, as well as a roster, agenda and transcript of the July 18, 2007 MedCAC meeting, are electronically available.[27]

5. Guidelines

According to the opening paragraph of section “3.5 Treatment of Renovascular Disease: Renal Artery Stenosis” of the American College of Cardiology/American Heart Association (ACC/AHA) 2005 Practice Guidelines:

“Treatment of renal arterial disease should serve to aid in the normalization of blood pressure and to preserve renal function, and possibly to reduce risk of cardiovascular events and mortality. Both medical (pharmacological) and revascularization strategies should be considered for patients with documented renal arterial disease. The relative efficacy and safety of medical and endovascular strategies remains an area of active clinical investigation.”[28]

The guidelines make specific recommendations for medical treatment of RAS, as well as indications for revascularization, catheter-based intervention and surgery.

Medical Treatment

1. Angiotensin-converting enzyme inhibitors are effective medications for treatment of hypertension associated with unilateral RAS. *(Class I, Level of Evidence: A)*[29]
2. Angiotensin receptor blockers are effective medications for treatment of hypertension associated with unilateral RAS. *(Class I, Level of Evidence: B)*
3. Calcium-channel blockers are effective medications for treatment of hypertension associated with unilateral RAS. *(Class I, Level of Evidence: A)*
4. Beta-blockers are effective medications for treatment of hypertension associated with RAS. *(Class I, Level of Evidence: A)*

Revascularization

1. Percutaneous revascularization may be considered for treatment of an asymptomatic bilateral or solitary viable kidney with a hemodynamically significant RAS. *(Class IIb, Level of Evidence: C)*
2. The usefulness of percutaneous revascularization of an asymptomatic unilateral hemodynamically significant RAS in a viable kidney is not well established and is presently clinically unproven. *(Class IIb, Level of Evidence: C)*

The Guidelines noted that "recommendations regarding the role of percutaneous revascularization of asymptomatic renal disease are made largely on the basis of expert opinion and are not based on evidence that treatment of asymptomatic RAS improves any renal or systemic outcome, including renal preservation, blood pressure, or cardiovascular morbidity or mortality:"

Hypertension

1. Percutaneous revascularization is reasonable for patients with hemodynamically significant RAS and accelerated hypertension, resistant hypertension, malignant hypertension, hypertension with an unexplained unilateral small kidney, and hypertension with intolerance to medication. *(Class IIa, Level of Evidence: B)*

Preservation of Renal Function

1. Percutaneous revascularization is reasonable for patients with RAS and progressive chronic kidney disease with bilateral RAS or a RAS to a solitary functioning kidney. *(Class IIa, Level of Evidence: B)*
2. Percutaneous revascularization may be considered for patients with RAS and chronic renal insufficiency with unilateral RAS. *(Class IIb, Level of Evidence: C)*

Congestive Heart Failure and Unstable Angina

1. Percutaneous revascularization is indicated for patients with hemodynamically significant RAS and recurrent, unexplained congestive heart failure or sudden, unexplained pulmonary edema (see text). *(Class I, Level of Evidence: B)*
2. Percutaneous revascularization is reasonable for patients with hemodynamically significant RAS and unstable angina (see text). *(Class IIa, Level of Evidence: B)*

Surgery for RAS

1. Vascular surgical reconstruction is indicated for patients with atherosclerotic RAS and clinical indications for intervention, especially those with multiple small renal arteries or early primary branching of the main renal artery. *(Class I, Level of Evidence: B)*

2. Vascular surgical reconstruction is indicated for patients with atherosclerotic RAS in combination with pararenal aortic reconstructions (in treatment of aortic aneurysms or severe aortoiliac occlusive disease). *(Class I, Level of Evidence: C)*

6. Professional Society Position Statements

In 2007, the American Society of Nephrology (ASN) Advisory Group on Hypertension published a review and position statement about ongoing controversies in RAS. Regarding outcomes and renovascular disease, the ASN stated:

“It is unknown whether RAS in an individual patient causes hypertension or contributes to declining renal function. Diagnostic tests to delineate this dilemma are not available. Guidelines regarding timing, evaluation, treatment, and follow-up are not formulated. The literature is confusing because of variable definitions of RAS and differences in studied populations.”[30]

Regarding specifically available published surgical, angioplasty and endovascular stent studies, the ASN stated that “the problems with generalizing these studies are several: (1) criterion for patient selection; (2) criterion for the diagnosis of RAS; (3) definition of outcome measures, and (4) lack of comparable control groups. When faced with the situation that ‘about one-third gets better, one-third gets worse, and one-third stays about the same’, clinical decision making becomes a hazardous undertaking.”

Looking to the future, the ASN stated that “clear, unambiguous definitions are necessary to permit a true assessment of the problem, its magnitude, and rational interventional approaches” and suggested that “a team of cardiologists and nephrologists should prospectively address these questions:

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- What is the prevalence of RAS in age-adjusted subgroups, namely patients with coronary disease, peripheral vascular disease, systolic and diastolic heart failure, proteinuric and nonproteinuric renal disease?

- How should ischemic nephropathy be defined so that agreement can be reached regarding who needs treatment and which strategy should be employed?

- What is the current natural history of RAS and what measure will most accurately detect progression of kidney disease?

- Which patients with RAS will benefit from revascularization? Specifically, do stents: (a) reduce BP; (b) slow progression of renal disease, and (c) prevent cardiovascular disease (CVD) outcomes?"

In conclusion the ASN noted: "An assessment should be conducted to prospectively compare nonselective overviews of the renal arteries with selective arteriography, magnetic resonance imaging angiography, and computerized tomography to determine the sensitivity, specificity, positive and negative predictive values of the brief overviews obtained during cardiac catheterization. In other words, is 'drive by' renal angiography a justifiable diagnostic test? We still do not know whether the treatment allows an improved outcome when these patients have their renin-angiotensin systems interrupted. Given the increase in cardiac and renal angiography procedures, and the fact that RAS as a cause of ischemic nephropathy and CKD [chronic kidney disease] is potentially reversible it is important to develop an integrated and informed approach to diagnose and treat RAS discovered incidentally at the time of cardiac catheterization.

Key Points:

1. Renal artery stenosis is associated with two clinical syndromes: hypertension and ischemic nephropathy.

2. Renal artery narrowing is necessary but not sufficient to cause progressive loss of GFR. There is not a 'tight' relationship between the extent of arterial narrowing and loss of GFR.

3. The most useful predictor of progressive loss of GFR is the initial GFR and renal atrophy.

4. Renal artery stenting may not result in prevention of loss of GFR because of irreversible, progressive parenchymal injury.

5. Prospective studies on the incidence, natural history, best practices for treating incidentally diagnosed renal artery stenosis are required.”[31]

7. Expert Opinion

In the “Controversies in Cardiovascular Medicine” section of the January 16, 2007 issue of *Circulation*, two sets of thought leaders in the field debated the pros and cons of renal angioplasty and stenting.[32,33]

Responding to their fellow co-investigators in the “Cardiovascular Outcomes in Renal Atherosclerotic Lesions” (CORAL) trial, which is presently recruiting internationally with ClinicalTrials.gov identifier: NCT00081731, the paired authors including the CORAL trial’s principal investigator in the “Case For…” and the CORAL trial’s study chair in the “Case Against…” responded to each other’s views as follows.

“Drs. Dworkin and Jamerson nicely outline limitations in the evidence supporting renal artery stent revascularization for patients with renal artery stenosis while concurrently highlighting the value of aggressive medical therapy. Undoubtedly, blood pressure control, lipid-lowering therapy, antiplatelet therapy, and other medical interventions are critically important in patients with established vascular disease, although the value of these medical therapies remains untested in patients with ischemic renal disease. Where we differ is in our apparent understanding of the potential for stent revascularization in this population. Whereas Drs. Dworkin and Jamerson rightly state that medical interventions have markedly reduced event rates in trials of primary and secondary prevention, the risk of patients with ischemic renal disease remains exceedingly high. Furthermore, successful revascularization sits in the tantalizing position of addressing multiple mechanisms that may drive cardiovascular and renal risk: neuroendocrine activation, progressive chronic kidney disease, and hypertension. Despite these interpretative differences, we both reach the same conclusion: The value of stenting needs to be established in patients who are aggressively medically managed and in a setting that avoids the methodological limitations of prior studies. Ongoing studies, including Stenting in Renal Dysfunction Caused by Atherosclerotic Renal Artery Stenosis (STAR) and Angioplasty and STent for Renal Artery Lesions (ASTRAL), are likely to provide insights into the effect of revascularization on the progression of chronic kidney disease. Cardiovascular Outcomes in Renal Atherosclerotic Lesions (CORAL), which is designed to address clinical events and to avoid the prior design limitations of crossover, patient selection, and treatment without stenting, should move opinions of the medical and interventional communities further toward consensus.”

“Drs. Cooper and Murphy admit that observational studies are often misleading, citing several famous examples of therapies that initially appeared to be markedly beneficial but were found to be completely without value or even harmful when examined in randomized trials. Nevertheless, they go on to present several uncontrolled case series of patients with renal artery stenosis that appear to show a benefit of revascularization. These data should be viewed with skepticism and are at best hypothesis generating. The other main arguments in favor of revascularization are theoretical. Renal ischemia leads to a pattern of neurohumoral activation involving the renin-angiotensin-aldosterone system, the systemic nervous system, and other circulating mediators and cytokines. What is lacking, however, is evidence that revascularization reverses these changes and is more effective than medical therapy, which also blocks the same systems in this regard. In fact, there are many reasons why revascularization may not be effective. Most patients are elderly with advanced atherosclerotic disease in other vascular beds and end-organ damage, including cardiac hypertrophy, ischemic cardiomyopathy, myocardial fibrosis, hypertensive glomerular sclerosis, tubulointerstitial fibrosis, atheroemboli, and microcerebral and macrocerebral vascular disease. These changes are likely to drive adverse outcomes even if renal perfusion improves. Finally, the authors acknowledge that the 3 randomized controlled trials, albeit flawed, fail to demonstrate any advantage of angioplasty and stenting over medical therapy. If medical decision making is to be evidence based, then angioplasty and stenting should be rarely, if ever, performed.”

8. Public Comments

CMS received 17 comments during the initial comment period for this reconsideration. One hundred thirty one references were cited in these comments to support various positions and opinions on the treatment of atherosclerotic RAS. These articles were all reviewed either via the Technology Assessment prepared for this analysis by AHRQ or through our own internal evidence review. A complete list of the references cited by commenters is provided in Appendix B of this document. References not specifically addressed in the AHRQ Technology Assessment or this decision memorandum were determined to be outside the scope of this reconsideration because they addressed issues of cost-effectiveness or imaging, included no relevant data, or were retrospective studies.

Coverage

The majority of commenters cite articles and studies, which CMS has reviewed in developing this proposed decision memorandum, to support their contentions that renal artery revascularization is beneficial and should be covered. Specifically, eight commenters highlight the benefit and/or superiority of renal artery stenting demonstrated by various studies as compared to renal PTA alone. Seven commenter support coverage of renal PTA with stenting by citing the benefits of renal PTAS as demonstrated in various articles and studies. One commenter identifies the benefit of renal PTA as compared to medical therapy and one commenter cites the benefits of renal revascularization in general to support coverage.

Four commenters assert that coverage should be provided in line with the American College of Cardiology/American Heart Association guidelines, which are referenced in Section 5 of this proposed decision memorandum.

Five commenters contend that data supports renal artery stenting as the standard of care for appropriate patients. One commenter states that surgical revascularization has been the standard of treatment for ARAS for many years.

Seven commenters contend that CMS should cover renal percutaneous transluminal angioplasty and stenting (PTRAS). Two commenters state that Medicare contractors' policies should be covered, one commenter asserts that the current policy should be maintained until more data are published and another commenter requests that CMS withdraw its plan to develop a new national coverage determination (NCD) for treatment of RAS.

One commenter states that this coverage reconsideration is a misguided response to perceptions that renal PTRAS is overutilized without clinical efficacy. One commenter asserts that it would be inappropriate for CMS to exclude coverage for PTRAS and another commenter contends that it is inappropriate to restrict patient access when the best treatment option is in the opinion of the treating physician.

Two commenters assert that angioplasty for non-ostial ARAS should be a reimbursable service as should bilateral renal interventions whether performed at the same time or separately. Two commenters contend that Medicare coverage should not be linked to the use of FDA approved stents for the renal arteries and the use of distal embolic protection devices should not be required for payment.

One commenter suggests that CMS cover renal stenting in patients with renal insufficiency or hypertension who take ≥ 3 medications and have renal stenosis > 60% and a gradient of > 15% in systolic pressure. Another commenter contends that coverage is appropriate for renal artery stenting in patients with > 70% stenosis, unilateral or bilateral, and chronic renal insufficiency or refractory hypertension with systolic blood pressure > 160 mmHg who take ≥ 3 mediations associated with a viable kidney. Another commenter asserts that CMS should consider patient populations with unusual indications that are unlikely to be studied in RCTs including patients with 1) flash pulmonary edema due to RAS; 2) aortic and/or renal artery dissection; 3) impingement on the renal artery by prosthetic devices; 4) prophylactic stenting prior to or in association with open or endovascular aortic aneurysm repair; and 5) solitary functioning kidneys.

Appropriate Patient Selection

One commenter states that renal artery interventions are appropriate in patients with narrowing of a renal artery of at least 50-60% with multi-drug hypertension, renal insufficiency or a history of flash pulmonary edema. Another commenter asserts that patients should display at least one clinical and one angiographic indication to justify a renal artery intervention. This commenter considers resistant hypertension, stage 3 or higher renal failure, or congestive heart failure to be appropriate clinical indications and renal stenosis ≥ 60% or invasive pressure measurements showing a systolic pressure gradient of ≥ 20 mmHg to be appropriate angiographic indications.

One commenter asserts that PTAS of ostial lesions is an important option for ARAS patients with refractory or uncontrolled hypertension, renal insufficiency, chronic kidney disease, unexplained heart failure or sudden pulmonary edema. One commenter contends that properly selected patients, those with a baseline serum creatinine < 2.0 mg/dL, bilateral ARAS, normal renal resistive indices, and no proteinuria, can experience improvements and/or stabilization in kidney function with renal artery revascularization, especially stenting. Another commenter states that patients that benefit from renal interventions have 1) inadequately controlled blood pressure; 2) worsening renal function with preserved renal parenchyma; 3) congestive heart failure or chronic renal failure; 4) recurrent or isolated pulmonary edema; or 5) fibromuscular dysplasia.

One commenter suggests that appropriate patients for renal artery revascularization are those with the characteristics of patients in the ASPIRE 2 registry and two other commenters contend that the eligibility criteria used in CORAL is the standard for appropriate performance of renal artery stenting. One commenter states that PTA alone should only be used to treat in-stent restenosis or fibromuscular dysplasia. Two commenters state that utilizing an “alternative to surgery” standard for renal artery stent placement is poorly considered and not justifiable.

Two commenters assert that the use of Doppler ultrasound to measure renal artery resistance is a good predictor of outcomes and may determine which patients will favorably respond to PTAS. One commenter contends that physicians should diagnose ARAS as discussed in the ACC/AHA guidelines.

Coverage and Clinical Trial Participation

Six commenters assert that the CMS coverage policy should actively encourage enrollment in the CORAL trial. One commenter suggests that since the current CMS policy allows payment for all renal artery interventions it may be creating a disincentive to enrollment in and impeding progress of CORAL. One commenter suggests that reimbursement be aligned with participation in clinical trials while another commenter contends that changing coverage would not impact patients who resist randomization and therefore would do little to increase enrollment in clinical trials. This commenter asserts that physicians' desires to generate more evidence will drive enrollment in CORAL and the completion of the trial.

Available Evidence

Three commenters reference several studies which were also reviewed for this reconsideration to establish the limitations of available data and the need for new data in order to determine the best treatment option for patients with renal artery stenosis.

Three commenters contend that more evidence is needed from well designed RCTs to identify patient populations and circumstances under which Medicare coverage of renal PTAS is appropriate. Two commenters assert that more evidence is needed to justify the large volume of renal artery interventions performed in the US. One commenter suggests that the FDA and CMS should collaborate on inviting major stent manufacturers to sponsor clinical trials investigating renal artery stenting with their own products to provide real world data that compliment data from RCTs. One commenter warns that the results of the CORAL trial may not be generalizable to the entire population.

Three commenters agree with the conclusions of the AHRQ technology assessment that there is no clear data to determine whether renal artery stenting is beneficial, but two commenters questions the inclusion of some medical therapy studies in this review because the medical therapies and revascularization regimes used in some of these studies predate advanced technologies and limits the validity of conclusions within the context of current medical practice. One commenter also states that conclusions specific to the benefits of medical therapy cannot be determined due to low patient compliance outside of trials and high levels of crossover from the medical therapy to the intervention arms in studies. One commenter suggests that CMS consider sources other than the AHRQ technology assessment when examining management strategies for RAS.

One commenter asserts that the body of evidence for renal artery revascularization continues to grow and is consistent with benefiting patients with RAS. One commenter contends that a lack of level 1 evidence for renal artery revascularization does not imply a lack of efficacy for these treatments. Another commenter asserts that there is no reason to believe that revascularization will better control blood pressure than medical therapy.

Physician Standards

Five commenters contend that physicians performing renal PTAS should meet training standards and/or participate in facility quality assurance programs.

Outpatient PTAS

Two commenters assert that most renal artery interventions are performed in outpatient or “short stay” (less than 24 hours) patients and outpatient renal PTAS is appropriate care in most cases.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act §1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member" (§ 1862(a)(1)(A)).

CMS focused its analysis upon whether the evidence is adequate to draw conclusions about health benefits of surgical and endovascular renal artery interventions (with concomitant medical management) compared to aggressive medical therapy alone for the treatment of patients with atherosclerotic RAS, whether the body of evidence is generalizable to and demonstrates improved health outcomes for the Medicare population; and whether Medicare national coverage of non-medical treatments for atherosclerotic RAS should be limited only to patients enrolled in qualified clinical research studies.

Is the evidence adequate to draw conclusions about health benefits of surgical and endovascular renal artery interventions compared to aggressive medical therapy alone for the treatment of patients with atherosclerotic RAS?

Evaluating the totality of evidence, CMS notes that published results exhibit uncertain internal validity due to emphasis upon intermediate or surrogate outcomes (such as BP) and do not demonstrate incrementally improved, long term health outcomes (kidney function, cardiovascular event rates, mortality or quality of life) that might be causally attributed to the surgical or endovascular renal artery interventions. Several factors, including the learning curve for interventionalists, the evolution of devices and procedures, and the lack of accepted uniform definitions, measurement techniques, and criteria for reporting patient selection, methods and outcomes result in an inability to compare studies, perform meta-analyses and draw solid evidence-based conclusions. The overall body of evidence also lacks consistency and reliability due to the lack of diagnostic tests or baseline characteristics that might accurately predict post-treatment renal function outcomes. Finally, since all available randomized trials are now of historic interest and do not reflect contemporary practice, there is uncertain external validity due to the limited applicability of published results to Medicare patients with typical comorbidities, providers (facilities/physicians) in community practice, and patient subgroups not represented in studied populations.

The RCTs identified evaluating safety and comparative effectiveness of treatment options are outdated and no longer applicable to the care of atherosclerotic RAS patients. Specifically, there is no published study directly comparing renal angioplasty and stenting to aggressive triple medical therapy utilizing currently available drugs for the treatment of atherosclerotic RAS. Further, no controlled trial has prospectively compared state-of-the-art medical therapy, endovascular therapy and open surgical renal artery reconstruction. While the landmark SHEP (Systolic Hypertension in the Elderly Program) trial[34] demonstrated that (in patients $\geq$ 60 years with systolic hypertension) medical control alone with antihypertensive stepped-care drug treatment reduced total mortality, cardiovascular mortality, stroke and heart failure rates, no comparable adequately powered, pivotal trial of endovascular or surgical therapy exists which shows any significant post-treatment improvement as compared to medical therapy alone for key long term health outcomes such as kidney function, cardiovascular events, mortality or quality of life.

The AHRQ 2006 and 2007 comparative effectiveness reviews focused upon extensive qualitative synthesis, applicability and limitations of available observational and experimental studies, rather than formal quantitative meta-analysis. The conclusions of the 2007 AHRQ update stated that "none of the studies evaluated the principal question of interest… The quality of the evaluated studies was limited due to inadequate reporting and/or collection of data, incomplete analyses, and often inconsistent use of interventions (e.g., combining angioplasty with and without stent); limited applicability due to restrictive patient eligibility or inadequate reporting; and limited power of studies due to small sample size. The evidence does not support one treatment approach over the other for the general population of people with ARAS." CMS has closely reviewed the AHRQ findings and conclusions and generally agrees with them. We particularly focused on the findings and conclusions derived from the best quality studies.

In its own review of the evidence, CMS carefully considered the presentations, public opinions, and majority vote of the panelists at the July 18, 2007 MedCAC meeting. The voting members' mean score of 2.92 (1 = not confident, 3 = uncertain and 5 = highly confident) reflected the panel's overall uncertainty about their confidence in the adequacy of the evidence to draw conclusions about safety and clinical effectiveness of surgical renal artery reconstruction (RAR) for the treatment of patients with atherosclerotic RAS, as well as the panel's uncertainty to lack of confidence (mean score = 2.31) regarding whether there are any improved key health outcomes attributable to surgical RAR co-intervention as compared to medical treatment alone. Similarly, mean scores of 2.92 and 2.85 reflected the MedCAC voting members' uncertainty regarding their confidence in the adequacy of the evidence to draw conclusions about safety and clinical effectiveness of PTRA and PTRAS for the treatment of patients with atherosclerotic RAS, as well as their lack of certainty (mean scores of 2.08 and 3.15) regarding whether there are any improved key health outcomes attributable to co-intervention respectively with PTRA or PTRAS compared to medical treatment alone.

Examining adverse events with surgical RAR as compared to aggressive medical treatment combined with PTRA and/or PTRAS, CMS notes that surgical co-interventions are limited by high procedural morbidity and mortality for most older patients with atherosclerotic renal artery stenoses that are not outweighed by any significant difference in beneficial outcomes. In Cherr and colleagues' (2002) study of 500 hypertensive patients with atherosclerotic RAS (mean age = 65 ± 9 years) who underwent surgical repair of renal artery disease, 23 patients (4.6% with significant and independent associations with both advanced age and congestive heart failure) died in the hospital or within 30 days following surgery; and perioperative morbidity (excluding deaths) occurred in 81 patients (16%).[35] Three subsequent smaller surgical series in 2004 and 2005 (also included in AHRQ's comparative effectiveness reviews) reported procedural or 30 day perioperative mortality rates ranging from 4 to 9%.[36,37,38]

In its evaluation of adverse events following endovascular renal artery procedures, CMS also carefully weighed the CORAL study chair's concluding comments to his co-investigators regarding PTRA and PTRAS: "Most patients are elderly with advanced atherosclerotic disease in other vascular beds and end-organ damage, including cardiac hypertrophy, ischemic cardiomyopathy, myocardial fibrosis, hypertensive glomerular sclerosis, tubulointerstitial fibrosis, atheroemboli, and microcerebral and macrocerebral vascular disease. These changes are likely to drive adverse outcomes even if renal perfusion improves. Finally, the authors acknowledge that the 3 randomized controlled trials, albeit flawed, fail to demonstrate any advantage of angioplasty and stenting over medical therapy. If medical decision making is to be evidence based, then angioplasty and stenting should be rarely, if ever, performed."[39,40]

Closely examining the safety of devices in current use, CMS notes that in 2002 the FDA's two PMA approvals for renal stents, indicated for use only after suboptimal or failed PTRA, each required a post-approval study and stated "failure to comply with the conditions of approval invalidates this approval order." Cordis' non-randomized, non-inferiority study was powered for a 10% loss to follow-up but was missing 26.4% of patients for measurement of its primary endpoint.[41] No record of completion or publication was found for Medtronic's required post-approval SOAR registry, and neither PMA for stenting after suboptimal or failed PTRA was reviewed by the FDA's Circulatory System Devices Panel.[42,43] In 2003 the FDA additionally mandated warnings in hepatobiliary stent labeling that safety and effectiveness of biliary stents for use in the vascular system have not been established. In 2004 a Class I recall was initiated for a situation in which there was reasonable probability that such vascular use of these stents would cause serious adverse health consequences or death.[44,45] Primary stenting, however, remains the most commonly performed endovascular co-intervention for atherosclerotic RAS. While there are no FDA approved devices for primary renal stenting, it is now clear that virtually all renal stenting procedures conducted in the U.S. are performed utilizing hepatobiliary stenting systems not indicated for use in the renal arteries.[46]

We do not believe that the evidence we have reviewed demonstrates whether health outcomes are improved with surgical renal artery reconstruction or percutaneous transluminal renal angioplasty with or without stenting.

Is the body of evidence generalizable to the Medicare population and providers in community practice?

The available randomized trials are now of historic interest and do not reflect contemporary practice. Therefore, external validity is uncertain due to the limited applicability of published results to Medicare patients with typical comorbidities, providers (facilities/physicians) in community practice, and patient subgroups not represented in studied populations.

Of the votes tallied where 1 = not confident, 3 = uncertain and 5 = highly confident, the MedCAC panelists lacked confidence in the applicability of published results to individual providers (facilities/physicians) in community practice (mean score = 2.15) and to unrepresented patient subgroups (mean = 1.69).

Additionally, of the RCTs reviewed and critically evaluated by both the Cochrane Collaboration and AHRQ, Plouin and colleagues (1998) most directly addressed and discussed generalizability of results from their widely referenced EMMA trial as follows:

"The external validity of this study is debatable. First, 1 in 3 eligible patients declined inclusion, mostly because of the patient's (or referring physician's) preference for angioplasty. We were unable to document subsequent outcome in patients eligible but not included. Included and nonincluded eligible patients did not differ, however, in terms of age, sex distribution, severity of hypertension, and renal function. Second, the total number of randomized patients was small. Third, efficacy and safety results could have been different in other hands or if renin-angiotensin inhibitors (in the control group) and intravascular stents (in the angioplasty group) had been used more frequently. The present trial was designed to assess the BP outcome of angioplasty and did not address long-term renal and cardiovascular outcomes in patients with atherosclerotic RAS. Considering renal outcomes, angioplasty seems attractive because it might prevent ischemic nephropathy and progression to renal artery thrombosis. Angioplasty with or without renal artery stenting in patients with progressive renal failure has limited BP-lowering potential, however, and it is associated with some mortality and a substantial morbidity. The efficacy and safety of angioplasty for stabilizing renal function in patients with atherosclerotic renovascular disease should therefore be assessed by specifically designed trials."[47]

Should Medicare national coverage of non-medical treatments for atherosclerotic RAS be limited only to patients enrolled in qualified clinical research studies?

The majority of MedCAC panelists (6 of the 9 voting members) agreed or strongly agreed that national coverage of any non-medical treatments for atherosclerotic RAS be limited only to Medicare patients enrolled in qualified clinical research studies. Requirements for protecting patients and determining whether clinical research is ethical have been proposed which delineate a systematic evaluative framework. Emanuel, *et al.'s* (2000) seven stated requirements include the research study's social or scientific value, scientific validity, fair subject selection, favorable risk-benefit ratio, independent review, informed consent, and respect for subjects.[48]

While some physicians may argue that renal artery stenting is the standard of care for patients with atherosclerotic RAS, true consensus regarding a best treatment strategy does not exist among all specialists caring for these patients. At the level of the expert community as a whole, such uncertainty over the efficacy and safety of a treatment [or alternative treatments] has been said to provide a proper basis for conducting an RCT.[49] This situation exists for treatment of atherosclerotic RAS, and a clinician/researcher once relevantly commented to colleagues:

"I would suggest that in many areas of medicine different expert clinicians often have different opinions as to the most appropriate treatment. Indeed, in life- or limb-threatening conditions, or when a treatment has many side effects, patients should be encouraged to seek a second opinion. In essence, the concept of clinical equipoise as originally articulated by Benjamin Freedman simply suggests that where second opinions are likely to disagree, physicians should be willing to include their patients in a randomized controlled trial. Rather than prohibiting the clinician from informing the patient of his or her personal beliefs, clinical equipoise simply asks the clinician to be honest, letting the patient know that a different but equally competent clinician might decide on a different course."[50]

In the absence of professional ethical responsibility, however, there is presently little incentive for investigators to conduct well-designed trials establishing safety and valid scientific evidence of effectiveness for renal artery revascularization procedures. Incomplete disclosure of serious adverse events as well as author, sponsor and negative publication biases combine to limit attempts to obtain a valid registry or results database. Discussing the pertinent ethical and scientific challenges in registering and expanding public access to clinical trial results, Zarin and colleagues (2007) stated that “it is not clear how the accuracy of non-peer-reviewed results and the appropriateness of the statistical analyses and interpretations could be validated with existing methods or resources. Concerns also exist about relying on sponsors or other data providers with vested interests in how the results are portrayed to submit narrative summaries of results. None of the policy proposals under discussion [for the reporting of both published and unpublished clinical research data in a government-run database] would provide registry staff with access to protocols or raw data, making the independent scientific review of database entries impossible. Without the ability to validate entries, selective reporting of trial results could still occur, thus undermining the key purpose of a results database.”[51]

Regarding how to responsibly move forward, vascular surgeon Dr. Edwards stated to his fellow MedCAC panelists (transcript page 222:20-22 [PDF, 644KB]): “I would certainly have clinical equipoise in putting patients into trials such as CORAL.” Definitions of equipoise, however, are variable[52] and some have postulated that the ethical basis for a clinical trial arises from uncertainty resting with the expert clinical community as a whole.[53] Accordingly, considering both the widespread off-label vascular usage of biliary stents and in order to determine how to best safeguard patients involved in future studies, CMS examined the U.S. Department of Health and Human Services regulations governing human research known as the Common Rule. This rule is codified at 45CFR46, Subpart A and stipulates that a full (rather than expedited) review and approval by an Institutional Review Board (IRB) must be obtained for trials of devices which are not being used in accordance with their cleared/approved labeling.[54]

CMS also noted in the “Data Element Definitions” at ClinicalTrials.gov that - so long as study patients are not yet being recruited - a trial may be submitted for registration prior to or while still awaiting IRB approval. Additionally, it is possible that only one facility’s IRB approval letter may be filed for internal administrative use in registering a multicenter trial. Since CMS reimburses individual providers rather than trials or trial sponsors, it is therefore essential for protection of Medicare patients considering enrollment that all research studies involving renal arterial stenting be fully reviewed and approved by each facility’s IRB. Likewise, reliance cannot be placed upon a single trial identifier number from an international trial registry which provides no direct oversight for patient safety, protection, monitoring or local clinical expertise at participating centers.

Of recognized observational and experimental approaches, RCTs have the greatest potential to minimize bias and provide valid evidence regarding the balance of benefits and harms attributable to surgical and/or endovascular co-interventions for the treatment of atherosclerotic RAS. To best protect the health and safety of affected Medicare patients, CMS notes that adequately informed patient consent is essential for all patient care. CMS recommends that for all renal artery revascularization procedures, whether performed within or outside of RCTs or other clinical research studies, informed patient consent should be obtained which:

1. Accurately explains the purpose and duration of the study, its procedures, potential risks and benefits, treatment alternatives (i.e., medical therapy alone versus combined medical therapy plus endovascular and/or surgical co-interventions), need for long term follow-up, as well as any financial or intellectual conflicts of interest, such that a patient understands this information and its relevance to his or her own clinical situation, and can make a voluntary decision whether to enroll and continue to participate; and

2. Discloses to prospective Medicare patients the following relevant information:

    -
    - The May 2004 FDA Class I recall (a situation in which there is reasonable probability that use of or exposure to a violative product will cause serious adverse health consequences or death) for a transhepatic biliary stent, which noted that vascular use of these stents has not been cleared by the FDA and which strongly recommended that physician use of these stents be limited to FDA-approved uses only;
    - The July 2007 MedCAC panelists determination that there is overall uncertainty about: a) the adequacy of the evidence to draw conclusions about safety and clinical effectiveness of surgical and endovascular renal artery interventions for the treatment of patients with atherosclerotic RAS; b) the applicability of published results to Medicare patients with typical comorbidities, providers (facilities/physicians) in community practice, and patient subgroups not represented in published studies; and c) whether there are any improved key health outcomes attributable to surgical and endovascular co-interventions as compared to medical treatment alone; and
    - Availability of CMS's decision memorandum for renal artery revascularization procedures to be read and discussed by Medicare patients and their physicians at: http://www.cms.hhs.gov/mcd/viewtrackingsheet.asp?id=202.

CMS recommends that any hospital facility at which RCTs or other clinical research studies are performed should:

1. Conduct its own full review and have Institutional Review Board (IRB) approval for the study at its facility.

2. Ensure that the study is internationally registered and provide on each study's ClinicalTrials.gov webpage a hyperlink to a publicly available, up-to-date protocol; and

3. Stipulate that the study have primary endpoints (≥ 12 months duration and not surrogate outcomes) seeking to clarify or establish both long term health outcomes as well as adverse effects following aggressive medical therapy plus percutaneous endovascular and/or open surgical renal artery revascularization as compared to aggressive medical therapy alone.

Finally, CMS recommends that all RCTs or other clinical research studies enrolling Medicare patients specify the following:

1. Study purpose and hypothesis;

2. Inclusion and exclusion criteria fully describing the experimental and control arms;

3. Use of (or investigation to clarify or establish) standardized diagnostic criteria, uniform operational definitions and validated measurement techniques for patient selection, methods and outcomes;

4. Use of blinded outcome assessors;

5. Dates and explanations for all study protocol changes;

6. Design phase and analytic strategies to minimize the effects of confounding and/or concurrent provision of other therapies (co-interventions);

7. How adequate statistical power has been assured to enable drawing clinically meaningful conclusions regarding the study's pre-specified primary and secondary endpoints;

8. How results are to be generalized to the general Medicare population and affected Medicare subpopulations; and

9. Method and timing for (at least) annual reporting of preliminary results plus public release and/or peer-reviewed publication of final results.

In summary, after more than a decade of inconsistent uncontrolled observational studies and negative randomized trials which began recruiting in the 1980s and early 1990s, there is general uncertainty regarding any potential health benefit of either surgical or endovascular renal artery revascularization as compared to aggressive medical therapy alone. No adequately powered RCT has established that improved health outcomes can be causally attributed to these co-interventions for any well-defined clinical indication, and the body of evidence is of overall poor quality and limited applicability to Medicare patients with typical comorbidities in community practice. Surgical renal artery revascularization is limited by high perioperative morbidity and mortality; and hepatobiliary stents, which are commonly used off-label for renal stenting, have been the focus of an FDA Class I recall, and can result in severe procedural complications such as embolization (van de Ven, 1999). Public comments following the announcement of CMS opening this NCD also reiterate this uncertainty. In light of this, CMS proposes to make no change in the current NCD.

CMS wishes to foster the necessary long term health outcomes research and establish evidence-based treatment strategies by encouraging affected Medicare patients to enroll in rigorously designed RCTs at IRB approved hospital facilities. Absent any reported additional serious patient harms, further national coverage reconsideration of renal artery revascularization procedures will ethically and scientifically depend upon peer-reviewed publication and critical evaluation of convincing new RCT evidence.

IX. Proposed Decision

The Centers for Medicare and Medicaid Services (CMS) proposes to make no change in the NCD addressing PTA of the renal arteries (Pub. 100-3, 20.7, B1).

We are requesting public comments on this proposed determination pursuant to Section 1862(1) of the Social Security Act. After considering the public comments and any additional evidence, we will make a final determination and issue a final decision memorandum.

Appendix A: General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine whether: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients. An improved health outcome is one of several considerations in determining whether an item or service is reasonable and necessary.

CMS normally divides the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the relevance of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's risks and benefits.

The issues presented here represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has unique methodological aspects.

1. Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to help ensure adequate numbers of patients are enrolled to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias)
- Co-interventions or provision of care apart from the intervention under evaluation (confounding)
- Differential assessment of outcome (detection bias)
- Occurrence and reporting of patients who do not complete the study (attrition bias)

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study's selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess the evidence.

2. Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens, and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease, and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing, and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage decisions for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation), and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations because one of the goals of our determination process is to assess health outcomes. We are interested in the results of changed patient management not just altered management. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

3. Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Improved health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. For most determinations, CMS evaluates whether reported benefits translate into improved health outcomes. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

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[1] http://www.cms.hhs.gov/mcd/viewncd.asp?ncd_id=20.7&ncd_version=4&basket=ncd%3A20%2E7%3A4%3APercutaneous+Transluminal+Angioplasty+%28PTA%29

[2] FDA device classification depends on intended use of the device and also upon indications for use. Classification is risk-based, i.e., the risk the device poses to the patient. Class I includes devices with lowest risk and Class III includes those with greatest risk (http://www.fda.gov/cdrh/devadvice/313.html)

[3] Cavanaugh (2006)

[4] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=814&showFR=1

[5] http://www.fda.gov/cdrh/devadvice/pma/clinical_studies.html#determination

[6] http://www.fda.gov/cdrh/pdf/P890017S010.html

[7] http://www.fda.gov/cdrh/pdf2/P020007.html

[8] Cavanaugh (2006)

[9] Cooper, et al. (2006)

[10] http://www.fda.gov/cdrh/recalls/recall-050404.html

[11] Sos (2006)

[12] Webster, *et al.* (1998)

[13] Plouin, *et al.* (1998)

[14] van Jaarsveld, *et al.* (2000)

[15] Webster, *et al.* (1998)

[16] Plouin, *et al.* (1998)

[17] Nordmann, *et. al.* (2003)

[18] Balk, *et al.* (2006)

[19] http://www.cms.hhs.gov/faca/downloads/id39c.pdf (Dr. Balk's 2007 MedCAC presentation, pp. 19-46).

[20] Tier I studies were RCTs that compared angioplasty with stent placement to aggressive medical therapy (no studies met this criterion). Tier II studies were RCTs that compared angioplasty with or without stent to medical therapy with at least 6 months of follow-up. Tier III studies were other comparative studies that compared angioplasty or vascular surgery to medical therapy (regardless of follow-up time). Tier IV studies were noncomparative cohort (pre-post) studies of interventions of interest.

[21] Weibull, *et al.* (1993)

[22] Webster, *et al.* (1998)

[23] Plouin, *et al.* (1998)

[24] van de Ven, *et al.* (1999)

[25] van Jaarsveld, *et al.* (2000)

[26] Uzzo, *et al.* (2002)

[27] http://www.cms.hhs.gov/mcd/viewmcac.asp?where=index&mid=39

[28] Hirsch, *et al.* (2006)

[29] *ACC/AHA Classification of Recommendations:*

- *Class I*: Conditions for which there is evidence for and/or general agreement that a given procedure or treatment is beneficial, useful, and effective.
- *Class II*: Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
- *Class IIa*: Weight of evidence/opinion is in favor of usefulness/efficacy.
- *Class IIb*: Usefulness/efficacy is less well established by evidence/opinion.
- *Class III*: Conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.

Level of Evidence:

- *Level of Evidence A*: Data derived from multiple randomized clinical trials or meta-analyses.
- *Level of Evidence B*: Data derived from a single randomized trial or nonrandomized studies.
- *Level of Evidence C*: Only consensus opinion of experts, case studies or standard of care.

[30] Levin, *et al.* (2007)

[31] Levin, *et al.* (2007)

[32] Cooper and Murphy (2007)

[33] Dworkin and Jamerson (2007)

[34] SHEP Cooperative Research Group (1991)

[35] Cherr, *et al.* (2002)

[36] Alhadad, *et al.* (2004)

[37] Marone, *et al.* (2004)

[38] Galaria, *et al.* (2005)

[39] Cooper and Murphy (2007)

[40] Dworkin and Jamerson (2007)

[41] Rocha-Singh, *et al.* (2005)

[42] http://www.fda.gov/cdrh/pdf/P890017S010.html

[43] http://www.fda.gov/cdrh/pdf2/P020007.html

[44] http://www.fda.gov/cdrh/pdf3/K033394.pdf

[45] http://www.fda.gov/cdrh/recalls/recall-050404.html

[46] Cavanaugh (2006)

[47] Plouin, *et al.* (1998)

[48] Emanuel, *et al.* (2000)

[49] Sackett (2000)

[50] Shrier (2001)

[51] Zarin, *et al.* (2007)

[52] Discussing feasibility of RCTs and relative benefits of alternative treatment options, Young, *et al.* (2004) noted equipoise was a term used to reflect “a state of genuine clinical uncertainty, when preferences for alternative therapies are poised or equally balanced, and neither treatment option is clearly superior. Equipoise can work at the level of the individual clinician (clinical equipoise) or within the clinical community (collective equipoise).” It has also been argued that only a research subject’s evaluation is morally relevant and the patient need not be equally poised or indifferent between treatment options to volunteer for randomization, and Veatch (2007) has stated that “all that is needed is adequately informed, free, and unexploited [patient] consent.”

[53] "Consider a situation in which there was no individual physician uncertainty, with half the physicians considering treatment A preferable, and half preferring B… It is just this state of (un)certainty that calls out for evidence as to which is the better treatment. It is important for the individual physician to set aside his or her opinion, bias or 'certainty' in deference to the reasoned uncertainty that exists within the larger community of experts." (Shapiro and Glass 2000)

[54] According to *Research Categories* section (1)(b) in the list of categories authorized by section 110 of the Common Rule, an expedited IRB review (rather than a full or convened IRB review) may only be performed for research involving no more than minimal risk and only for "research on medical devices for which (i) an investigational device exemption application (21CFR812) is not required [812.2(c)]; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling."

(http://www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm)

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http://clinicaltrials.gov/ct/info/resources (Clinical Trials information)

http://clinicaltrials.gov/ct/show/NCT00081731?order=3 (CORAL trial registration)

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http://www.cms.hhs.gov/faca/downloads/id39c.pdf (Dr. Balk's MedCAC presentation of updated 2007 Comparative Effectiveness Review, pp. 19-46)

http://www.cms.hhs.gov/mcd/viewmcac.asp?where=index&mid=39 (July 18, 2007 MedCAC meeting homepage)

http://www.cms.hhs.gov/mcd/viewncd.asp?ncd_id=20.7&ncd_version=4&basket=ncd%3A20%2E7%3A4%3APercutaneous+Transluminal+Angioplasty+%28PTA%29 (Medicare NCD Manual for PTA 20.7)

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http://www.fda.gov/cdrh/pdf2/P020007.html (Medtronic AVE Bridge™ Extra Support Over-The-Wire (OTW) Renal Stent System, PMA Number P020007, December 18, 2002)

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